Tetrahedron 69 (2013) 3054–3060

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of pyrrole-fused chromanones via one-pot multicomponent reactions

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ARTICLE INFO

Article history:
Received 4 November 2012
Received in revised form 10 January 2013
Accepted 28 January 2013
Available online 12 February 2013

Keywords:
3-Acetyl-2*H*-chromen-2-ones
Isocyanides
Dihydrochromeno[3,4-*c*]pyrrole-1,4-dione
Tandem reactions

ABSTRACT

We have developed one-pot method for the synthesis of functionalized novel pyrrole-fused chromanones. A variety of 5-hydroxy-*N*-substituted-2*H*-dihydrochromeno[3,4-*c*]pyrrole-2-ones were obtained in moderate to good yields via condensation of 2-hydroxybenzaldehydes and ethyl acetoacetate with isocyanides in ethanol. The proof of the structure relies on analytical investigation and X-ray crystallography. These reactions presumably proceed via reaction of the in situ generated 3-acetyl-2*H*-chromen-2-one intermediates with isocyanides through Michael addition/intramolecular cyclization/oxidation tandem sequences.

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1. Introduction

The so-called multicomponent reactions (MCRs) are one-pot processes in which at least three or more different simple substrates react for the preparation of target materials.[1] These reactions, which have gained much attention over the past years, frequently occur not through a single-step procedure, but rather by several sequential steps or multicomponent cascade or domino reactions.[2] Simplicity, greater efficiency and atom economy with generation of molecular complexity and diversity in a one-pot transformation are some advantages of these reactions. As an important subclass of MCRs, the isocyanide based multicomponent reactions (IMCRs) are processes in which an isocyanide is used as one of the starting materials in order to obtain new compounds.[3] The pioneering work of Ugi is the most popular IMCR in which a carboxylic acid, a primary amine, an aldehyde, and an isocyanide react in a one-pot manner to afford an *N*-substituted acyl amino-amide containing four independently varying groups.[4]

A number of isolated biologically active natural products are known to contain the 5-hydroxy-3-pyrrolin-2-one moiety. These include fusarin C (**1**, potent mycotoxin),[5] epolactaene (**2**, effective in promoting neural outgrowth and arresting the cell cycle at the G0/G1 phase in a human neuroblastoma cell line),[6] oteromycin (**3**, a novel antagonist of the ETB receptor),[7] and azaspirene (**4**, a novel angiogenesis inhibitor)[8] (Fig. 1).

The known properties of heterocycles containing the 5-hydroxy-3-pyrrolin-2-one moieties along with the documented

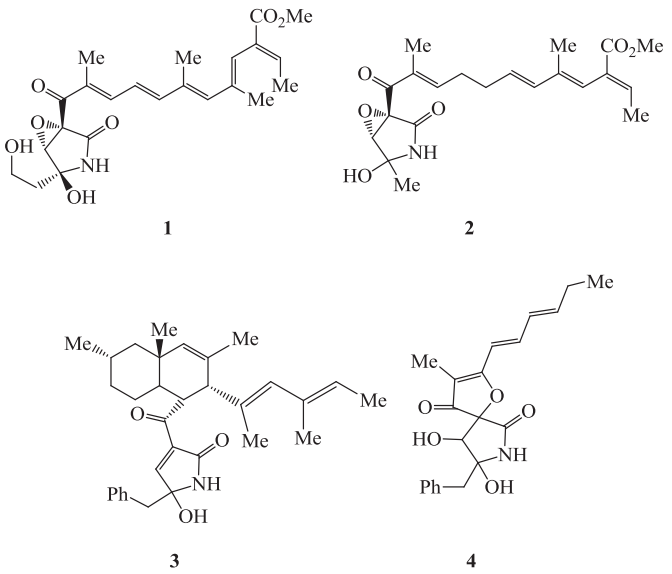

Fig. 1. Structures of fusarin C (**1**), epolactaene (**2**), oteromycin (**3**), and azaspirene (**4**).

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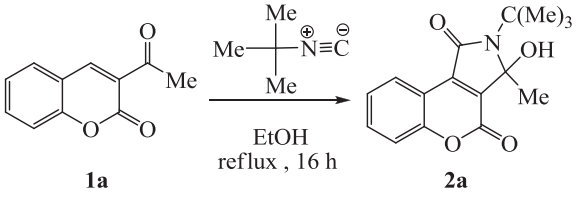
http://dx.doi.org/10.1016/j.tet.2013.01.085

multiple biological activities of coumarins in treating various cancer, cardiovascular, and rheumatic diseases[9] prompted us to undertake a study on the synthesis of novel heterocyclic scaffolds containing the 5-hydroxy-3-pyrrolin-2-one motif, fused with chromanones. Based on the known participation method of the in situ generated quinone methides obtained from 4-hydroxycoumains and aldehydes in a [4+1] cycloaddition reaction with isocyanides,[10] we decided to carry out the similar [4+1] cycloaddition of the in situ generated 3-acetyl-2*H*-chromen-2-ones with isocyanides as a convenient alternative to the synthesis of coumarin-based heterocycles. Herein, we report the synthesis of novel 2-hydroxy-*N*-substituted-2*H*-dihydrochromeno[3,4-*c*]pyrrole-2-ones via a one-pot, three component reaction of a variety of 2-hydroxybenzaldehydes with ethyl acetoacetate and *tert*-butyl, cyclohexyl or 1,1,3,3-tetramethylbutyl isocyanides in ethanol.

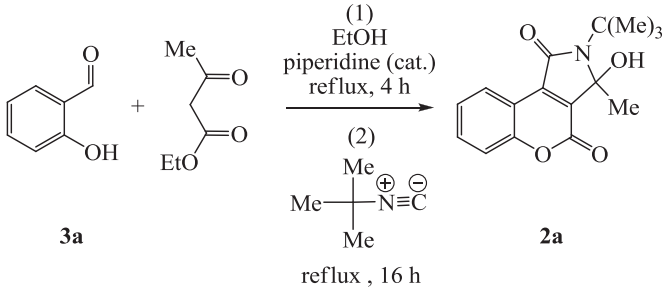
2. Results and discussion

3-Acetyl-2*H*-chromen-2-one (**1a**) was used for our early investigation. Indeed, **2a** was isolated as the sole reaction product upon treatment of **1a** with an equimolar amount of *tert*-butyl isocyanide in EtOH at reflux within 16 h (Scheme 1).



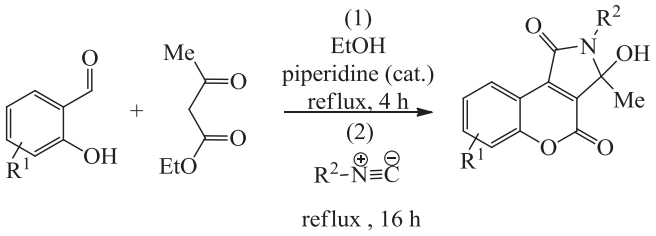
Scheme 1. Formation of **2a** from the reaction of **1a** with *tert*-butyl isocyanide.

Our later studies revealed that **2a** could be synthesized in a one-pot reaction if **1a** prepared in situ from piperidine-catalyzed condensation of salicylaldehyde (**3a**) with ethyl acetoacetate in EtOH at reflux within 4 h, is treated with an equimolar amount of *tert*-butyl isocyanide at reflux within 16 h (Scheme 2). Therefore, the utility of 3-acetyl-2*H*-chromen-2-one (**1a**) in the initial reaction was confirmed.



Scheme 2. One-pot synthesis of **2a** from **3a**.

This new method was then applied to a range of 2-hydroxybenzaldehydes (**3a**–**d**) and *tert*-butyl, cyclohexyl or 1,1,3,3-tetramethylbutyl isocyanides (Scheme 3, Table 1). The structures of **2a**–**l** were deduced by elemental analysis, MS, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. For example, part of the ^{1}H NMR spectrum of **2b** exhibited characteristic Me and OH signals at δ 1.89 (3H, s) and 3.05 (1H, s), respectively. The ^{1}H-decoupled ^{13}C NMR spectrum of **2b** showed 16 distinct signals, including two characteristic peaks at δ 160.4 and 163.8 due to two C=O groups, in agreement with the proposed structure. Unambiguous evidence for the proposed structure of **2b** was finally obtained by single crystal X-ray diffraction analysis (Fig. 2).[11]



Scheme 3. One-pot synthesis of **2a**–**l** from **3a**–**d** and isocyanides.

We propose the following mechanistic consideration to account for the formation of hydroxyamide **2a** on the basis of the previously reported works (Scheme 4).[12] Upon the formation of 2-aminofuran (**I$_1$**) as the initially generated product, it may combine with triplet oxygen quite rapidly to afford hydroperoxide **I$_2$** and molozonide **I$_3$**, respectively. Similar to that of the known classical ozonalysis reaction, **I$_3$** may be fragmented to compound **I$_4$**. Rapid conversion of **I$_4$**, affords **I$_5$** and finally hydroxyamide **2a** by the well-known process of disproportionation.[13]

The effect of introducing either a strong electron-donating (EDG) or electron-withdrawing group (EWG) into the salicylaldehyde ring is to decrease the product yields (entries 7 to 12, Table 1). On the other hand, whereas unsubstituted salicylaldehydes afford the corresponding products in highest yields (entries 1 to 3, Table 1), those bearing modest electron-withdrawing groups produce a less pronounced reduction in yields (entries 4 to 6, Table 1). This behavior supports the suggested mechanism for the formation of the initially generated product **I$_1$** (Scheme 3) if the isocyanide addition to the double bond of **1a** (first step, Scheme 3), or the subsequent cyclization process (second step, Scheme 3) becomes rate limiting for EDGs and EWGs, respectively. Therefore, obtaining lower yields of **2g**–**l** is anticipated.

3. Conclusion

In conclusion, a one-pot, three component reaction for the synthesis of pyrrole-fused chromanone derivatives was described. Overall, a number of 5-hydroxy-*N*-substituted-2*H*-dihydrochromeno[3,4-*c*]pyrrole-2-ones were obtained in moderate to good yields via condensation of 2-hydroxybenzaldehydes and ethyl acetoacetate with isocyanides in ethanol. These new structures broaden the chromenone scaffolds and many of them may represent interesting pharmacophores.

4. Experimental section

4.1. General information

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer, in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500-AVANCE spectrometer at 500 (^{1}H) and 125 MHz (^{13}C) using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm). Mass spectra of the products were obtained with an HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

4.2. Representative procedure for the synthesis of 2a–l

To a stirring solution of piperidine (0.170 g, 20 mol %) in EtOH (10 mL) was added 2-hydroxybenzaldehyde derivative (1.0 mmol)

Table 1
Results obtained for the formation of **2a**–**l**

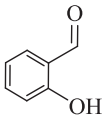
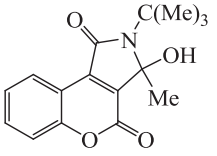
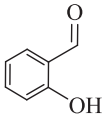
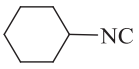
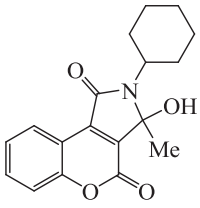
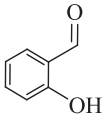
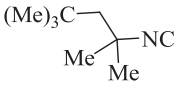
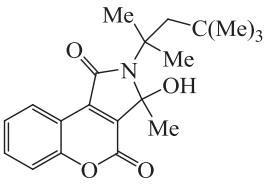
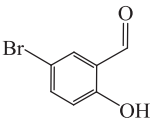
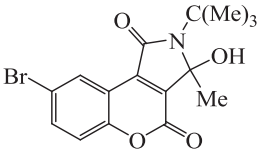
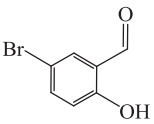
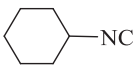
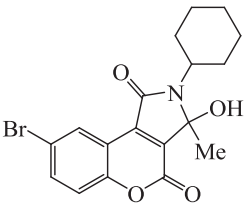
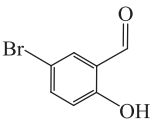
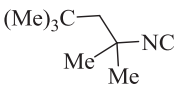
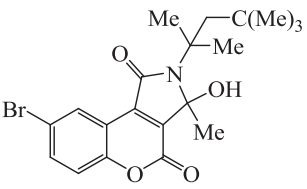
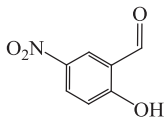
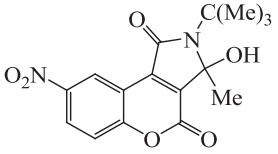
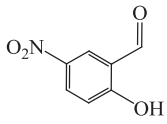
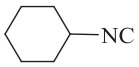
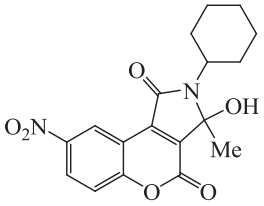
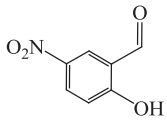
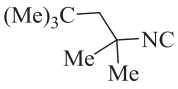
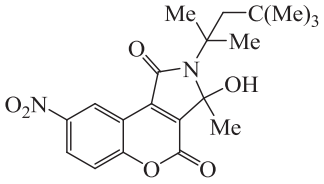
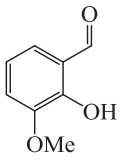
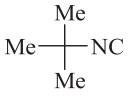
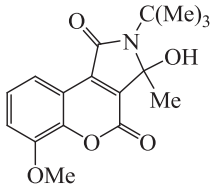
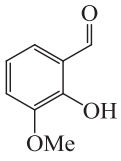
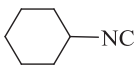
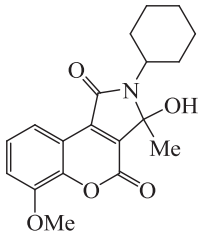
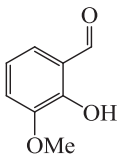
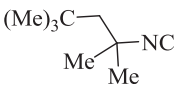
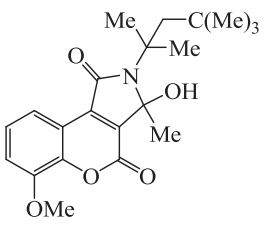
Entry	Aldehyde	Isocyanide	Product	Yield (%)
1	 **1a**	$(Me)_3C–NC$	 **2a**	64
2	 **1a**		 **2b**	65
3	 **1a**		 **2c**	65
4	 **1b**	$(Me)_3C–NC$	 **2d**	62
5	 **1b**		 **2e**	63
6	 **1b**		 **2f**	63

Table 1 (*continued*)

Entry	Aldehyde	Isocyanide	Product	Yield (%)
7	 **1c**	$(Me)_3C-NC$	 **2g**	49
8	 **1c**		 **2h**	50
9	 **1c**		 **2i**	55
10	 **1d**		 **2j**	52
11	 **1d**		 **2k**	59
12	 **1d**		 **2l**	60

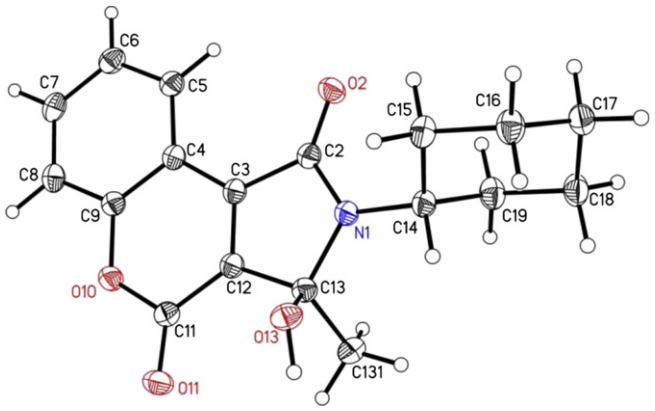
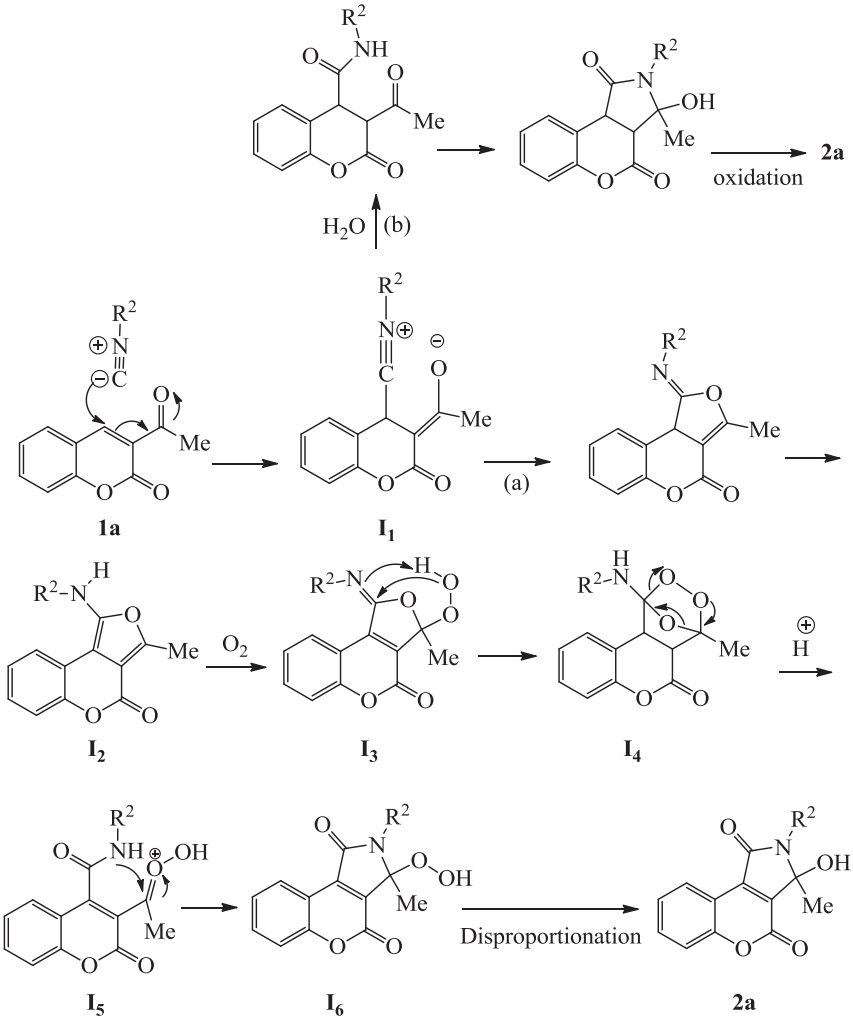


Fig. 2. X-ray crystal structure of compound **2b**.

*4.2.1. 2-tert-Butyl-3-hydroxy-3-methyl-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2a**).* White solid (184 mg, 64%); mp 171–173 °C; [found: C, 66.49; H, 6.18; N, 4.67. $C_{16}H_{17}NO_4$ requires C, 66.89; H, 5.96; N, 4.88%]; R_f (33% EtOAc/hexane) 0.40; ν_{max} (KBr) 3411 (OH), 1731 (C=O), 1683 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.66 (9H, s, CMe_3), 2.64 (3H, s, Me), 3.16 (1H, s, OH), 7.36–7.40 (2H, m, Ar), 7.60–7.64 (1H, m, Ar), 8.60 (1H, dd, *J* 5.2, 2.0 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.9 (Me), 26.2 (CMe_3), 52.9 (CMe_3), 88.2 (C_3), 109.4, 122.2, 123.4, 128.2, 129.4 (Ar), 140.5 (C_{3a}), 145.4 (C_{9b}), 150.5 (Ar), 160.4 (C=O), 163.4 (C=O); *m*/*z* (EI, 70 eV) 287 (8, M^+), 272 (20), 215 (86), 97 (20), 58 (100%).

*4.2.2. 2-Cyclohexyl-3-hydroxy-3-methyl-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2b**).* White solid (203 mg, 65%); mp 173–175 °C; [found: C, 68.69; H, 6.18; N, 4.67. $C_{18}H_{19}NO_4$ requires C, 68.99; H, 6.11; N, 4.47%]; R_f (33% EtOAc/hexane) 0.41; ν_{max} (KBr)



Scheme 4. Proposed mechanism for the formation of **2a**.

and ethyl acetoacetate (0.130 g, 1.0 mmol) and the mixture was heated at reflux for 4 h. Isocyanide (1.0 mmol) was then added and the mixture was heated at reflux for another 16 h. After completion as indicated by TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, eluent: 1:3 *n*-hexane/EtOAc) to afford the products **2a**–**l**.

3474 (OH), 1723 (C=O), 1694 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.20–2.50 (10H, m, $5CH_2$ of cyclohexyl), 1.89 (3H, s, Me), 2.80 (1H, s, OH), 3.50 (1H, m, CHN of cyclohexyl), 7.36–7.40 (2H, m, Ar), 7.60–7.64 (1H, m, Ar), 8.60 (1H, dd, *J* 6.4, 1.6 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.7 (Me), 25.2, 26.2, 26.3, 30.0, 30.0 (CH_2), 52.8 (CHN of cyclohexyl), 88.2 (C_3), 114.9, 125.1, 125.8, 132.2, 133.4 (Ar), 137.3

(C_{3a}), 145.5 (C_{9b}), 150.5 (Ar), 160.4 (C=O), 163.8 (C=O); *m*/*z* (EI, 70 eV) 314 (17, M^++1), 296 (80), 215 (60), 98 (100), 56 (80%).

*4.2.3. 3-Hydroxy-3-methyl-2-(2,4,4-trimethylpentan-2-yl)-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2c**).* White solid (223 mg, 65%); mp 150–152 °C; [found: C, 69.56; H, 7.18; N, 4.17. $C_{20}H_{25}NO_4$ requires C, 69.95; H, 7.34; N, 4.08%]; R_f (33% EtOAc/hexane) 0.43; ν_{max} (KBr) 3274 (OH), 1717 (C=O), 1642 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.07 (9H, S, CMe_3), 1.65 (6H, s, CMe_2), 1.78 (2H, s, CH_2), 2.64 (3H, Me), 3.17 (1H, s, OH), 7.36–7.40 (2H, m, Ar), 7.60–7.64 (1H, m, Ar), 8.60 (1H, dd, *J* 8.40, 6.4, 1.6 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.9 (Me), 27.9, 31.0 (CMe_2), 31.6, 31.7 (CMe_3), 54.0 (CCH_2C), 57.7 (CMe_2), 88.2 (C_3), 109.3, 122.2, 123.4, 128.2, 129.4 (Ar), 140.5(C_{3a}), 145.5 (C_{9b}), 150.5 (Ar), 160.4, 163.4 (C=O); *m*/*z* (EI, 70 eV) 343 (8, M^+), 272 (20), 215 (86), 97 (20), 58 (100%).

*4.2.4. 8-Bromo-2-tert-butyl-3-hydroxy-3-methyl-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2d**).* White solid (226 mg, 62%); mp 183–185 °C; [found: C, 52.69; H, 4.18; N, 3.67. $C_{16}H_{16}Br\ NO_4$ requires C, 52.48; H, 4.40; N, 3.82%]; R_f (3% EtOAc/hexane) 0.50; ν_{max} (KBr) 3279 (OH), 1715 (C=O), 1639 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.66 (9H, s, CMe_3), 2.07 (3H, s, Me), 3.06 (1H, s, OH), 7.28 (1H, d, *J* 9.0 Hz, Ar), 7.71 (1H, dd, *J*=9.0, 2.4 Hz, Ar), 8.83 (1H, d, *J*=2.4 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.9 (Me), 26.2, (CMe_3), 52.9 (CMe_3), 88.3 (C_3), 122.2, 123.4, 128.2, 129.4, 134.3 (Ar), 135.4 (C_{3a}), 145.5 (C_{9b}), 150.4 (Ar), 160.31 (C=O), 163.3 (C=O); *m*/*z* (EI, 70 eV) 367 (M^++2 [^{81}Br], 15), 365 (M^+ [^{79}Br], 15), 350 (43), 295 (68), 223 (17), 58 (100%).

*4.2.5. 8-Bromo-2-cyclohexyl-2,3-dihydro-3-hydroxy-3-methylchromeno[3,4-c]pyrrole-1,4-dione (**2e**).* Greenish solid (246 mg, 63%); mp 189–190 °C; [found: C, 55.49; H, 4.41; N, 3.47. $C_{18}H_{18}Br\ NO_4$ requires C, 55.12; H, 4.63; N, 3.57%]; R_f (33% EtOAc/hexane) 0.53; ν_{max} (KBr) 3335 (OH), 1736, 1660 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.20–2.50 (10H, m, $5CH_2$ of cyclohexyl) 1.89 (3H, s, Me), 2.80 (1H, s, OH), 3.50 (1H, m, CHN of cyclohexyl), 7.28 (1H, d, *J*=8.8 Hz, Ar), 7.71 (1H, dd, *J*=8.8, 2.4 Hz, Ar), 8.83 (1H, d, *J*=2.4 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.7 (Me), 25.2, 26.2, 26.3, 30.0, 30.1 (CH_2), 52.8 (CHN of cyclohexyl), 88.2 (C_3), 114.9, 120.4, 127.1, 127.8, 133.4 (Ar), 137.3 (C_{3a}), 145.5 (C_{9b}), 150.5 (Ar), 160.4 (C=O), 163.8 (C=O); *m*/*z* (EI, 70 eV) 395 (M^++2 [^{81}Br], 18), 393 (M^+ [^{79}Br], 18), 376 (34), 295 (80), 98 (100), 56 (75%).

*4.2.6. 8-Bromo-3-hydroxy-3-methyl-2-(2,4,4-trimethylpentan-2-yl)-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2f**).* Greenish solid (265 mg, 63%); mp 174–175 °C; [found: C, 56.49; H, 5.71; N, 3.37. $C_{20}H_{24}BrNO_4$ requires C, 56.88; H, 5.73; N, 3.32%]; R_f (3% EtOAc/hexane) 0.52; ν_{max} (KBr) ν_{max} 3295 (OH), 1710 (C=O), 1665 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.07 (9H, s, CMe_3), 1.65 (6H, s, CMe_2), 1.78 (2H, s, CH_2), 2.64 (3H, s, Me), 3.17 (1H, s, OH), 7.28 (1H, d, *J*=9.2 Hz, Ar), 7.71 (1H, dd, *J*=9.2, 2.4 Hz, Ar), 8.83 (1H, d, *J*=2.4 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.9 (Me), 27.9, 31.0 (CMe_2), 31.6, 31.7 (CMe_3), 54.0 (CCH_2C), 57.7 (CMe_3), 88.2 (C_3), 122.2, 123.4, 128.2, 129.4, 134.3 (Ar), 135.5 (C_{3a}), 145.5 (C_{9b}), 150.5 (Ar), 160.3 (C=O), 163.3 (C=O); *m*/*z* (EI, 70 eV) 423 (M^++2 [^{81}Br], 8), 421 (M^+ [^{79}Br], 8), 366 (15), 350 (43), 295 (68), 58 (100%).

*4.2.7. 2-tert-Butyl-3-hydroxy-3-methyl-8-nitro-2,3-dihydrochromeno [3,4-c]pyrrole-1,4-dione (**2g**).* Brownish solid (163 mg, 49%); mp 159–160 °C; [found: C, 57.49; H, 4.71; N, 8.47. $C_{16}H_{16}\ N_2O_6$ requires C, 57.83; H, 4.85; N, 8.43%]; R_f (33% EtOAc/hexane) 0.35; ν_{max} (KBr) 3395 (OH), 1706 (C=O), 1639 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.66 (9H, s, CMe_3), 2.64 (3H, s, Me), 3.16 (1H, s, OH), 7.55 (1H, d, *J*=8.0 Hz, Ar), 8.52–8.61 (2H, m, Ar); δ_C (100 MHz, $CDCl_3$), 22.9 (Me), 26.2, 52.9 (CMe_3), 88.2 (C_3), 122.2, 123.4, 128.2, 129.4 (Ar) 140.5 (C_{3a}), 144.5 (C_{9b}) 145.5, 157.4 (Ar), 160.4 (C=O), 163.4 (C=O); *m*/*z* (EI, 70 eV) 332 (8, M^+), 318 (33), 260 (100), 191 (20), 58 (36%).

*4.2.8. 2-Cyclohexyl-3-hydroxy-3-methyl-8-nitro-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2h**).* Brownish solid (179 mg, 50%); mp 169–170 °C; [found: C, 60.39; H, 4.99; N, 7.77. $C_{18}H_{18}N_2O_6$ requires C, 60.33; H, 5.06; N, 7.82%]; R_f (33% EtOAc/hexane) 0.36; ν_{max} (KBr) 3417 (OH), 1692 (C=O), 1649 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.20–2.50 (10H, m, $5CH_2$ of cyclohexyl) 1.89 (3H, s, Me), 2.78 (1H, s, OH), 3.47–3.54 (1H, m, CHN of cyclohexyl), 7.55 (1H, d, *J*=9.2 Hz, Ar), 8.52–8.61 (2H, m, Ar); δ_C (100 MHz, $CDCl_3$), 22.7 (Me), 25.2, 26.2, 26.3, 30.0, 30.1 (CH_2), 52.9 (CHN of cyclohexyl), 88.3 (C_3), 122.2, 123.4, 128.2, 129.3 (Ar), 140.5 (C_{3a}), 144.4(C_{9b}), 145.5, 157.4 (Ar), 160.4 (C=O), 163.4 (C=O); *m*/*z* (EI, 70 eV) 358 (8,M^+), 344 (35), 260 (100), 191 (20), 58 (35%).

*4.2.9. 3-Hydroxy-3-methyl-8-nitro-2-(2,4,4-trimethylpentan-2-yl)-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2i**).* Brownish solid (213 mg, 55%); mp 154–155 °C; [found: C, 61.72; H, 6.12; N, 7.27. $C_{20}H_{24}N_2O_6$ requires C, 61.84; H, 6.23; N, 7.21%]; R_f (33% EtOAc/hexane) 0.37; ν_{max} (KBr) 3390 (OH), 1672, 1659 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.07 (9H, s, CMe_3), 1.65 (6H, s, CMe_2), 1.78 (2H, s, CH_2), 2.65 (3H,s, Me), 3.17 (1H, s, OH), 7.55 (1H, d, *J*=6.0 Hz, Ar), 8.52–8.61 (2H, m, Ar); δ_C (100 MHz, $CDCl_3$), 22.9 (Me), 27.9, 31.0 (CMe_2), 31.6, 31.7 (CMe_3), 54.0 (CCH_2C), 57.7 (CMe_3), 88.2 (C_3), 122.2, 123.4, 128.2, 129.4 (Ar) 140.5 (C_{3a}), 144. 4(C_{9b}), 145.5, 157.5 (Ar), 160.3, 163.4 (C=O); *m*/*z* (EI, 70 eV) 388 (8, M^+), 332 (35), 318 (33), 260 (100), 191 (20), 58 (35%).

*4.2.10. 2-tert-Butyl-3-hydroxy-6-methoxy-3-methyl-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2j**).* Greenish solid (165 mg, 52%); mp 189–190 °C; [found: C, 64.49; H, 6.11; N, 4.47. $C_{17}H_{19}NO_5$ requires C, 64.34; H, 6.03; N, 4.41%]; R_f (33% EtOAc/hexane) 0.25; ν_{max} (KBr) 3317 (OH), 1752, 1675 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.66 (9H, s, CMe_3), 2.64 (3H, s, Me), 3.16 (1H, s, OH), 4.0 (3H, s, OMe), 7.29 (1H, d, *J*=8.4 Hz, Ar), 7.69–7.72 (1H, dd, *J*=7.6, 2.8 Hz, Ar), 8.83 (1H, d, *J*=1.2 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.9 (Me), 26.2, 52.9 (CMe_3), 55.9 (OMe), 88.2 (C_3), 112.4, 122.2, 128.2, 129.4, 137.3 (C_{3a}), 144.5 (C_{9b}), 147.5, 150.5 (Ar), 160.4, 163.4 (C=O); *m*/*z* (EI, 70 eV) 317 (8, M^+), 302 (35), 245 (80), 114 (34), 97 (35), 58 (100%).

*4.2.11. 2-Cyclohexyl-3-hydroxy-6-methoxy-3-methyl-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2k**).* Greenish solid (202 mg, 59%); mp 209–210 °C; [found: C, 66.49; H, 6.11; N, 4.07. $C_{19}H_{21}NO_5$ requires C, 66.46; H, 6.16; N, 4.08%]; R_f (33% EtOAc/hexane) 0.26; ν_{max} (KBr) 3347 (OH), 1742, 1685 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.20–2.50 (10H, m, $5CH_2$ of cyclohexyl) 1.89 (3H, s, Me), 2.80 (1H, s, OH), 3.47–3.54 (1H, m, CHN of cyclohexyl), 4.00 (3H, s, OMe), 7.28 (1H, d, *J*=7.2 Hz, Ar), 7.71 (1H, dd, *J*=7.2, 2.4 Hz, Ar), 8.82 (1H, d, *J*=2.4 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.7 (Me), 25.2, 26.2, 26.3, 30.0, 30.1 (CH_2), 52.9 (CHN of cyclohexyl), 58.2 (OMe), 88.2 (C_3), 114.9, 120.4, 127.1, 127.8, 133.4 (Ar) 137.3 (C_{3a}), 145.4 (C_{9b}), 150.4 (Ar), 160.4, 163.9 (C=O); *m*/*z* (EI, 70 eV) 343 (8, M^+), 329 (50), 245 (100), 175 (28), 98 (70), 56 (32%).

*4.2.12. 3-Hydroxy-6-methoxy-3-methyl-2-(2,4,4-trimethylpentan-2-yl)-2,3-dihydrochromeno[3,4-c]pyrrole-1,4-dione (**2l**).* Greenish solid (224 mg, 60%); mp 174–175 °C; [found: C, 67.43; H, 7.23; N, 3.66. $C_{21}H_{27}NO_5$ requires C, 67.54; H, 7.29; N, 3.75%]; R_f (33% EtOAc/hexane) 0.27; ν_{max} (KBr) 3317 (OH),1712, 1695 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$), 1.07 (9H, s, CMe_3), 1.65 (6H, s, CMe_2), 1.78 (2H, s, CH_2), 2.65 (3H, s, Me), 3.10 (1H, s, OH), 4.00 (3H, s, OMe), 7.28 (1H, d, *J*=7.6 Hz, Ar), 7.71 (1H, dd, *J*=7.6, 2.4 Hz, Ar), 8.83 (1H, d, *J*=2.4 Hz, Ar); δ_C (100 MHz, $CDCl_3$), 22.9 (Me), 27.9, 31.0 (CMe_2), 31.6, 31.7 (CMe_3), 54.0 (CCH_2C), 57.7 (CMe_3), 59.7 (OMe), 88.3 (C_3), 112.4,

122.2, 128.2, 129.4 (Ar) 137.3 (C_{3a}), 144.5 (C_{9b}) 147.5, 150.5 (Ar), 160.3, 163.4 (C=O); *m*/*z* (EI, 70 eV) 374 (33, M^++1), 302 (35), 245 (80), 114 (34), 97 (35), 58 (100%).

Acknowledgements

The authors acknowledge the University of Tehran for financial support of this research.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.085. These data include MOL files and InChiKeys of the most important compounds described in this article.

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11. Crystallographic data for **2b** have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 907693. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: 44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).
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